



Adjustable and fixed dosing with budesonide/formoterol via a single inhaler in asthma patients: the ASSURE study

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Summary Patient-guided management of asthma using adjustable dosing of budesonide/formoterol in a single inhaler (Symbicort[®]) was compared with fixed dosing in an open-label, multicentre, randomised study. Patients, uncontrolled on an inhaled corticosteroid (ICS) or controlled on an ICS and a long-acting β_2 -agonist, entered a 4-week run-in period and received budesonide/formoterol (80/4.5 or 160/4.5 μ g), 2 inhalations b.i.d. Following randomisation, the fixed-dosing group ($n = 764$) continued this regimen for a further 12 weeks. The adjustable-dosing group ($n = 775$) could step down to 1 inhalation b.i.d. if symptoms were controlled, and, at early signs of worsening symptoms, promptly step up to 4 inhalations b.i.d. for ≤ 2 weeks.

During run-in, National Heart, Lung and Blood Institute symptom-severity grading was maintained in 60% and improved in 31% of patients, clinic peak flow increased from 400 to 419 l/min ($P < 0.001$), and health-related quality of life (overall MiniAQLQ) improved from 4.6 to 5.4 ($P < 0.001$). Patients effectively used the adjustable-dosing regimen; 79% reduced budesonide/formoterol dosage and, compared with fixed dosing, the number of inhalations were significantly lowered (3.2 vs. 3.8 inhalations/day, $P < 0.05$). Both regimens were well tolerated. In both groups, symptom control was maintained or improved in 85–86% of patients, and 94% experienced no treatment failures. Consistent with current guidelines, adjustable maintenance dosing with budesonide/formoterol in a single inhaler provides effective asthma control at reduced medication doses.

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Introduction

Asthma is a chronic inflammatory condition characterised by variability of symptoms, airway calibre, bronchial hyper-responsiveness and treatment

requirements; intermittent exacerbations can occur, which, if severe, can be life threatening.

National and international treatment guidelines recognise the need to control asthma with the lowest adequate doses of medication,^{1,2} with inhaled corticosteroids (ICSs) established as the cornerstone of treatment. Budesonide is a well-established ICS that is effective and well tolerated for maintenance treatment of asthma across a wide

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dose range (200–1600 µg daily^{3,4}). Furthermore, Foresi et al.⁵ demonstrated that, in patients taking low-dose budesonide (100 µg twice daily), exacerbations could be effectively treated, at onset, by temporarily increasing the dose of budesonide to 1000 µg/day for 7 days.

The introduction of long-acting β_2 -agonists (LABAs) together with ICS, in asthma patients whose symptoms are uncontrolled by ICS alone, is now well established.^{1,2} Formoterol, added to inhaled budesonide improves asthma symptom control to a greater extent than increasing the dose of budesonide alone in patients over a wide range of asthma severity.^{6,7} Furthermore, budesonide together with formoterol has been shown to be well tolerated at high cumulative daily doses of 1920 and 54 µg, respectively,⁸ and at conventional doses long term.⁹ Formoterol has a rapid onset of action, within 3 min.¹⁰ It also produces dose-related bronchodilatation at single doses over the range of 6–48 µg.¹¹

Guidelines advocate the use of written guided self-management plans to allow patients to adjust their own treatment in accordance with the level of symptoms.^{1,2} Although guided self-management has been shown to result in clinically important improvements in asthma health outcomes,¹² thorough education and training of patients is required, and clear action plans using effective therapies are needed for success.^{13–15} However, the UK National Asthma Campaign survey¹⁶ identified considerable gaps in the information provided to patients when asthma was first diagnosed, and very few patients had written plans explaining when to take medication (6%) or what to do if asthma worsens (3%). From a survey of 517 UK asthma patients, Haughney et al.¹⁷ found that, although most patients (68%) felt comfortable about adjusting the dose of their inhaler without having to refer to a health professional, 81% had never been provided with a plan of how they could change their medication in response to varying symptoms.

Our hypothesis was that asthma can be effectively controlled by increasing and decreasing the dose of budesonide/formoterol, delivered twice daily from a single inhaler, to an appropriate level using a patient-driven self-management plan. The study compared a regimen of adjustable dosing with budesonide/formoterol in a single inhaler with traditional, fixed, twice-daily dosing of the same formulation in patients with asthma. The overall clinical benefits of treatment were evaluated in terms of the level of symptom control (treatment success) using National Heart, Lung and Blood Institute (NHLBI) definitions of symptom severity,¹⁸ and the proportion of patients experiencing treat-

ment failure. Additional comparisons between treatments were made of health-related quality of life (HRQoL), symptoms and lung function, and tolerability. The study aimed to recruit a large and diverse patient population suitable for ICS and LABA treatment from a range of practices across the UK, providing a robust assessment of the clinical effectiveness of the adjustable-dosing approach. This large study is the first to report the use of a self-management regimen in patients taking an ICS together with a LABA.

Methods

Study design

This randomised, open, parallel-group, multicentre study was conducted in 365 general practice and hospital centres across the UK. All patients initially entered a 4-week run-in period on budesonide/formoterol inhaler (Symbicort[®] Turbuhaler) 2 inhalations twice daily (Fig. 1). Patients taking budesonide 400 to <800 µg daily, or equivalent, before study entry received the budesonide/formoterol 80/4.5 µg formulation and patients taking budesonide 800–1600 µg daily, or equivalent, received the budesonide/formoterol 160/4.5 µg formulation. For this study, budesonide and beclometasone dipropionate (BDP) by pressurised metered-dose inhaler (pMDI) were considered of equivalent potency on a microgram for microgram basis. Because of the increased deposition of budesonide administered by Turbuhaler compared with pMDI, budesonide Turbuhaler doses were considered equivalent to fluticasone and twice those of BDP on a microgram for microgram basis. At 2 inhalations twice daily, patients taking budesonide/formoterol 80/4.5 µg received the

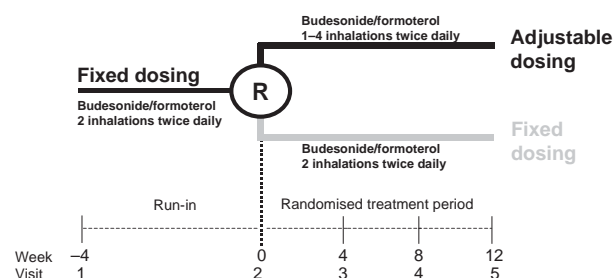


Figure 1 Study design: All patients received fixed dosing with budesonide/formoterol 80/4.5 or 160/4.5 µg 2 inhalations twice daily during the run-in and used the same strength of inhaler throughout the study. The dashed line indicates baseline at which patients were randomised (R) to two treatment groups.

same metered dose of budesonide (400 µg) and formoterol (24 µg) daily as by separate Turbuhalers. This also applied to patients taking higher strength budesonide/formoterol 160/4.5 µg, i.e., metered doses of budesonide 800 µg and formoterol 24 µg daily by separate Turbuhalers. Patients remained on the same strength of inhaler throughout the study. Pre-study reliever medications were discontinued and all patients used terbutaline sulphate 0.5 mg/dose (Bricanyl® Turbuhaler) as reliever medication throughout the study.

Patients ≥18 years of age, of either gender, were included in the study if they had a clinical diagnosis of asthma of at least 6 months duration, had been receiving ≥400 µg/day ICS, at a fixed dose, for at least 4 weeks, and budesonide/formoterol combination treatment was considered appropriate. Patients were recruited with either a history of previous stable symptom control taking an inhaled LABA and an ICS (symptoms ≤2 days per week, requiring ≤4 inhalations of reliever medication weekly and having ≤2 nights with nocturnal disturbance due to asthma in the previous month), or evidence of sub-optimal control if receiving an ICS and reliever medication alone (symptoms ≥2 days per week; or use ≥4 inhalations of reliever medication per week; or ≥2 nights with nocturnal asthma symptoms in the previous month; or a forced expiratory volume in 1 s (FEV₁) or peak expiratory flow (PEF) <80% of predicted normal,¹⁹ if measured). Patients were excluded if they had severe asthma (PEF <50% of predicted normal); or were receiving regular treatment with high-dose ICS (BDP or fluticasone propionate >2000 µg daily or budesonide >1600 µg daily), or current oral steroids, or nebulised therapy or β-blockers; or had used oral steroids for more than 10 days in the previous 3 months. Patients were also excluded if they had been hospitalised twice or more with asthma in the previous 12 months; or had suffered

an upper respiratory tract infection in the previous 4 weeks; or had other significant concomitant diseases. Other exclusion criteria were habitual overuse of β₂-agonists, pregnancy, planning pregnancy or lactation.

Following the run-in, patients were randomised to receive adjustable dosing (budesonide/formoterol 1–4 inhalations twice daily depending on asthma symptoms) (Table 1) or fixed dosing (budesonide/formoterol 2 inhalations twice daily) for 12 weeks. Patients in the adjustable-dosing group were instructed how to alter their therapy, according to their level of symptoms.

Approval was obtained from a Multicentre Research Ethics Committee and regional approvals from Local Research Ethics Committees for the sites involved in the study, and written informed consent was obtained from all patients.

Efficacy assessments

Patients were assessed for efficacy parameters at the beginning (visit 1) and end of the run-in (visit 2) and after 4, 8 and 12 weeks of randomised treatment. The patients completed diary cards each day throughout the study.

The primary efficacy variables were the number of treatment successes and treatment failures. Treatment success was assessed by determining the number of patients in each category of symptom control according to NHLBI definitions¹⁸ (mild intermittent, mild persistent, moderate persistent, severe persistent; Table 2). Patients were allocated to the most severe category for which they met at least one criterion.

Treatment failure was defined as one or more of the following: a serious asthma exacerbation leading to use of non-study medication (excluding a course of oral steroids lasting <5 days); hospitalisation because of asthma deterioration;

Table 1 Adjustable dosing: criteria for stepping up and stepping down.

Criteria for stepping up and stepping down	
Step down from 2 to 1, or from 4 to 2, inhalations twice daily	If the patient was unaware of recent disease deterioration, including a requirement for reliever medication on ≤2 days, and no night-time awakening, because of asthma during the previous week
Step up to 4 inhalations twice daily*	If the patient had required reliever medication ≥3 times during the day, or had night-time awakening because of asthma on 2 consecutive days

*Regardless of the dose the patient was receiving at the time. If there was no improvement after 14 days, or if symptom control deteriorated further, the patient was instructed to contact the investigator. A dose of 4 inhalations twice daily could be maintained for more than 14 days at the discretion of the investigator. Patients were instructed not to use more than 8 inhalations daily without consultation with their physician.

Table 2 Definitions of asthma symptom severity (based on NHLBI, 1997)¹⁸.

	Symptoms	Night-time symptoms	PEF
Severe persistent	Continuous: limited physical activity	Frequent	≤60% predicted Variability > 30%
Moderate persistent	Daily: use β_2 -agonist daily Attacks affect activity	> 1 time a week	> 60% to < 80% predicted Variability > 30%
Mild persistent	≥1 time a week but <1 time a day	> 2 times a month	≥80% predicted Variability: 20–30%
Mild intermittent	< 1 time a week asymptomatic and normal PEF between attacks	≤2 times a month	≥80% predicted Variability < 20%

PEF = peak expiratory flow.

emergency treatment, such as nebulised β_2 -agonist therapy or glucocorticosteroid injection; need for a course of oral steroids lasting 5 or more days; or lack of efficacy necessitating a change in asthma medication and withdrawal from the study. For patients in either group, two exacerbations requiring additional treatment were allowed, but a third exacerbation resulted in withdrawal from the study.

Secondary efficacy variables derived from diary-card data included morning and night-time PEF measurements, asthma-free days, night-time awakenings, use of reliever medication, daytime and night-time asthma symptom scores (assessed by the patient on a scale of 0 [defined as 'no asthma problems'] to 3 [defined as 'asthma problems prevent me from doing one or more activities' or 'asthma problems woke me up more than once in the night and stopped me from sleeping']) and number of study drug inhalations. PEF was also measured during each clinic visit.

At the beginning and end of the run-in and after 12 weeks of randomised treatment, patients completed a self-administered Mini Asthma Quality of Life Questionnaire (MiniAQLQ), with the overall score calculated as the mean score of 15 questions.²⁰ The MiniAQLQ comprises four domains, activity (ability to carry out active tasks), symptoms (distress due to asthma symptoms), emotional (emotional status) and environmental (symptoms within certain environments). An increase in score of >0.5 is considered indicative of a clinically relevant improvement in HRQL.²¹

Safety assessments

The number, type and severity of adverse events (AEs) were recorded throughout the study.

Statistics

Sample size was based on an estimate of there being an average of 11% treatment failures in the fixed-dosing group. This was estimated from the FACET study⁶ in which 7% of patients on high-dose budesonide had a severe exacerbation over 3 months, compared with 15% on low-dose budesonide. In order to detect a clinically relevant difference of 5%, e.g., 11% vs. 16%, with a power of 80%, it was calculated that 733 patients per group were required. It was aimed to enrol 1630 patients to allow for a 10% dropout during the run-in period.

All patients who were enrolled at visit 1 and received one dose of study drug were included in the safety analysis. All patients who were randomised and received at least one dose of study drug, and for which efficacy data were recorded, were included in the efficacy analysis. Between-group comparisons of treatment failure and treatment success were made using the Cochran–Mantel–Haenszel test. Secondary efficacy variables were summarised using descriptive statistics; the estimated mean difference (and 95% CIs) between groups for change from baseline (defined as the last 10 days of the run-in period) were calculated.

Analysis of HRQL was based on a published method.²⁰

Results

Of the 1719 patients who were recruited to the run-in period, a total of 1553 patients were randomised to receive treatment, and of these, 1539 received at least one dose of randomised treatment (775 adjustable dosing, 764 fixed dosing) and were included in the efficacy analysis. Reasons for non-randomisation were: AEs ($n = 61$), non-eligibility ($n = 16$), lack of therapeutic response to budesonide/formoterol ($n = 25$) and loss during run-in ($n = 21$); and miscellaneous ($n = 43$).

Demographic and clinical characteristics were similar for the two randomised-treatment groups (Table 3). Ninety-eight per cent of patients (both groups) were Caucasian. The distribution of patients according to severity of asthma symptoms was also similar; almost half of the patients had moderate-persistent symptoms at enrolment, with 6% having severe-persistent symptoms. Duration of asthma was >1 year in 97% of the patients and >5 years in 76% of the patients. The majority of patients in both groups received BDP as the pre-study ICS (58% adjustable dosing, 55% fixed dosing); 68% overall had been using pMDIs. Prior to the study, 39% of patients in the adjustable-dosing group and 42% in the fixed-dosing group were taking

a LABA. Asthma was less severe in patients who received budesonide/formoterol 80/4.5 μg than those receiving 160/4.5 μg during the randomised-treatment phase of the study—56% of patients allocated 80/4.5 μg at visit 1 were classified as having mild-intermittent or mild-persistent asthma symptoms compared with 41% of patients allocated 160/4.5 μg .

Efficacy results during the run-in period

At the end of the run-in (visit 2), after 4 weeks of treatment with budesonide/formoterol 2 inhalations twice daily, 31% of all patients showed an improvement in asthma symptom control compared with visit 1 (Fig. 2). There was a significant overall improvement in severity status for patients ($P < 0.001$ Wilcoxon's signed-rank test), with a greater proportion of patients (32% vs. 18%) categorised with mild-intermittent symptoms and fewer with severe- or moderate-persistent asthma (37% vs. 52%). The majority of shift in severity was from moderate- to mild-persistent or mild-intermittent asthma, and from mild-persistent to mild-intermittent asthma. This improvement in asthma symptom severity status was also reflected in the mean overall MiniAQLQ score, which increased during the run-in from 4.6 ($\pm \text{SD } 1.2$) to 5.4 ($\pm \text{SD } 1.1$) ($P < 0.0001$). There were clinically important improvements in the means of all four domains of the MiniAQLQ; activity from 5.2 ($\pm \text{SD } 1.3$) to 5.8

Table 3 Demographic and clinical characteristics at randomisation.

	Adjustable dosing	Fixed dosing
Number of patients	782	771
Male/female	299/483	315/456
Mean age (years)	48.7	48.0
Range	18–87	18–81
Mean clinic PEF (l/min)* (SD)	416 (113)	423 (119)
80/4.5 μg	433 (114)	439 (117)
160/4.5 μg	403 (110)	411 (119)
Use of SABA for symptom relief during the run-in (% days)	44	46
80/4.5 μg	40	44
160/4.5 μg	47	47
Mean pre-study ICS dose† (μg)	674	670
Pre-study LABA;‡ patients; (%)	302 (39)‡	323 (42)‡
Budesonide/formoterol inhaler; patients; (%)		
80/4.5 μg	337 (43)	331 (43)
160/4.5 μg	445 (57)	440 (57)

PEF = peak expiratory flow, ICS = inhaled corticosteroids, SABA = short-acting β_2 -agonist, LABA = long-acting β_2 -agonist.

* $n = 775$ and 764 for the adjustable- and fixed-dosing groups, respectively.

† $n = 772$ and 755 for the adjustable- and fixed-dosing groups, respectively.

‡Includes LABA and combination ICS/LABA products.

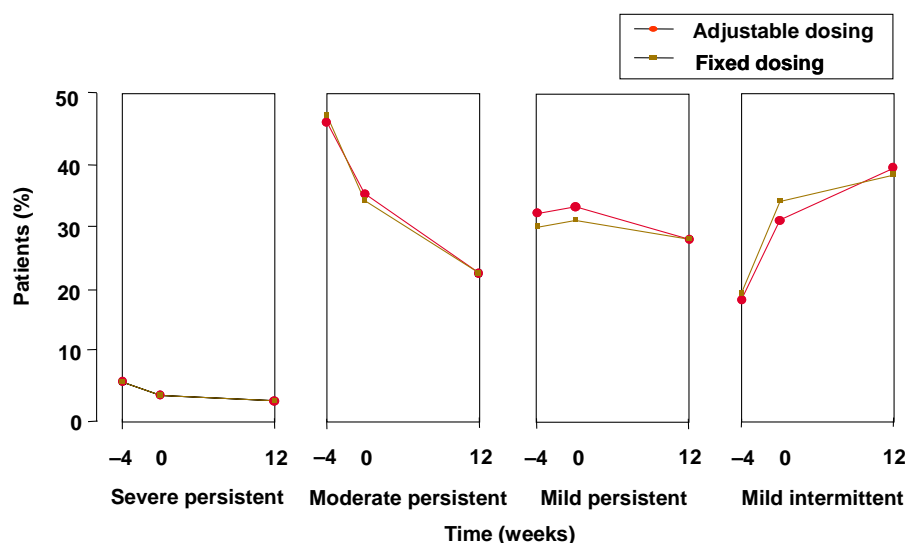


Figure 2 The proportion of patients showing improvement or worsening of asthma during the run-in (weeks -4-0) and randomised-treatment period (weeks 0-12), as indicated by a change in asthma symptom severity level as defined by NHLBI guidelines.¹⁸

(\pm SD 1.2) ($P < 0.0001$); symptoms from 4.4 (\pm SD 1.2) to 5.3 (\pm SD 1.2) ($P < 0.0001$); emotional from 4.3 (\pm SD 1.6) to 5.2 [\pm SD 1.5] ($P < 0.0001$); environment from 4.4 [\pm SD 1.4] to 5.1 [\pm SD 1.4] ($P < 0.0001$). Mean clinic PEF also increased clinically and statistically significantly from 400 to 419 l/min during the run-in period ($P < 0.001$).

Results for the randomised-treatment comparison

Ability of patients to use self-management plan

In the adjustable-dosing group, most patients (604, 79%) reduced the dose of their medication at some point during the randomised period; 69% and 53% used 2 inhalations/day or less for at least 7 and 28 consecutive days, respectively. Of the patients who reduced their dose of study medication, 121 (20%) had one or more dosage increases during the randomised-treatment period. Overall, 217 (28%) of patients increased their dosage to 8 inhalations/day at least once during the randomised period; with 111 of these stepping up only once; the median length of step up was 10 days. On average, patients recorded that they used 2 inhalations/day or less of study medication for half of the randomised-treatment period.

Efficacy results

For the majority of patients in both groups (86-87%), the level of asthma symptom control achieved during the run-in was either maintained or improved during the randomised period (Fig. 2).

The symptom severity levels in the adjustable- and fixed-dosing groups were improved in 29% and 28%, respectively, and maintained in 57% in both dosing groups. At the end of the study, a greater proportion of patients in both groups were categorised with mild-intermittent symptoms (39% vs. 30%) and fewer patients were categorised with severe- or moderate-persistent symptoms than at randomisation (29% vs. 38%).

In both treatment groups, 94% of patients did not experience a treatment failure (Fig. 3) with the most common reason for treatment failure in both treatment groups being a need for a course of oral steroids lasting 5 or more days. Only 2% of patients in the adjustable-dosing group and 3% of patients in the fixed-dosing group withdrew from the study because of treatment failure. There was no significant difference in the proportion of patients experiencing treatment failures within each group for patients receiving 80/4.5 or 160/4.5 μ g budesonide/formoterol.

Secondary measures

Secondary efficacy variables either improved slightly or were relatively stable during the randomised-treatment period (Table 4). Patients in both treatment groups showed a higher proportion of asthma-free days and fewer nocturnal awakenings compared with the run-in period. The improvements in symptom scores and MiniAQLQ score observed during the 4-week run-in were maintained throughout the randomised-treatment period in both groups (Table 4), with no differences between the groups.

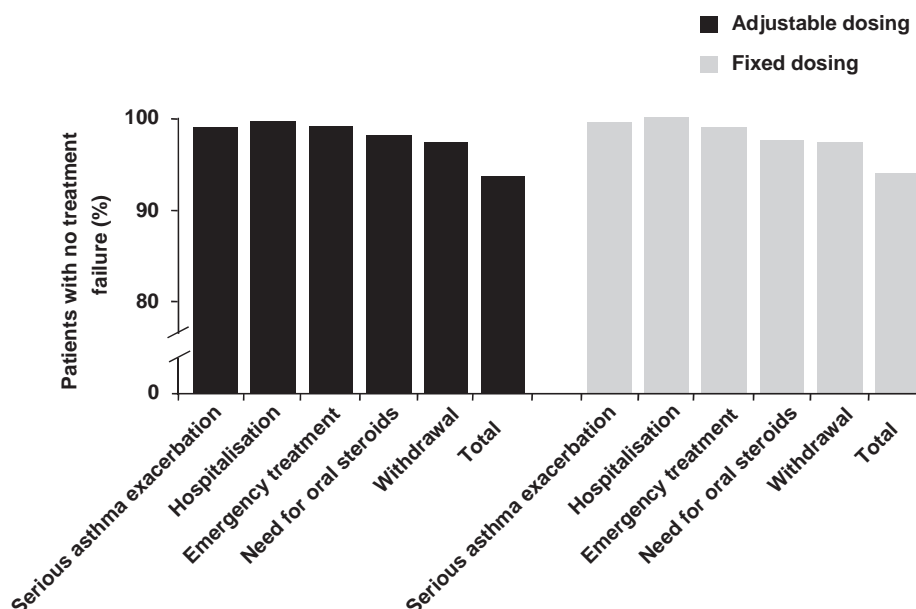


Figure 3 The proportion of patients not experiencing treatment failure during the randomised treatment phase of the study. Reasons for treatment failure are shown along the x-axis.

Table 4 Secondary efficacy variables: changes from baseline (last 10 days of run-in) to endpoint (week 12).

	Adjustable dosing (mean)		Fixed dosing (mean)		Difference in change between groups (adjustable minus fixed) [†] (Mean and 95% confidence intervals)
	Baseline	Change at endpoint	Baseline	Change at endpoint	
Asthma-free days (%)	45.3	3.2	43.7	3.4	0.2 (−2.6, 3.0)
Nights with nocturnal awakenings (%)	8.5	−1.1	9.7	−0.9	−0.7 (−1.9, 0.4)
Use of reliever medication [‡]	1.1	−0.2	1.2	0	−0.2 (−0.3, −0.1)*
Reliever-free days (%)	64.0	1.9	61.8	2.2	0.5 (−2.4, 3.4)
Average total symptom score	0.8	0.0	0.8	−0.1	0.0 (0.0, 0.1)
Mean MiniAQLQ score	5.4 [§]	0.0	5.4 [§]	0.0	0.0 (−0.1, 0.0)
Mean morning PEF (l/min)	390	−2.0	393	2.7	−4.8 (−8.0, −1.7)**
Mean evening PEF (l/min)	395	−2.3	397	1.7	−4.0 (−7.1, −0.9)**

* $P < 0.05$ in favour of adjustable-dosing group vs. fixed-dosing group.

** $P < 0.05$ in favour of fixed-dosing group vs. adjustable-dosing group.

PEF = peak expiratory flow, MiniAQLQ = Mini Asthma Quality of Life Questionnaire.

[†]Based on ANCOVA model, which included terms for treatment group and strength of budesonide/formoterol inhaler.

[‡]Average inhalations/day.

[§]Baseline values were obtained from the questionnaire completed at visit 2.

The overall improvement in PEF observed during the run-in was maintained in both arms after randomisation; both morning and evening PEF (recorded by patients) increased in the fixed-dosing group by approximately 2 l/min, and decreased in the adjustable-dosing group by a similar amount. Although there were statistically signifi-

cant differences in the change in morning and evening PEF during the randomised-treatment period (4–5 l/min), this difference was very small (1% baseline). Furthermore, there was no significant difference between the two groups in clinic-measured PEF during the randomised-treatment period.

Doses of budesonide/formoterol and reliever medication

The mean number of inhalations/day of budesonide/formoterol over the course of the randomised period was lower in the adjustable-dosing group

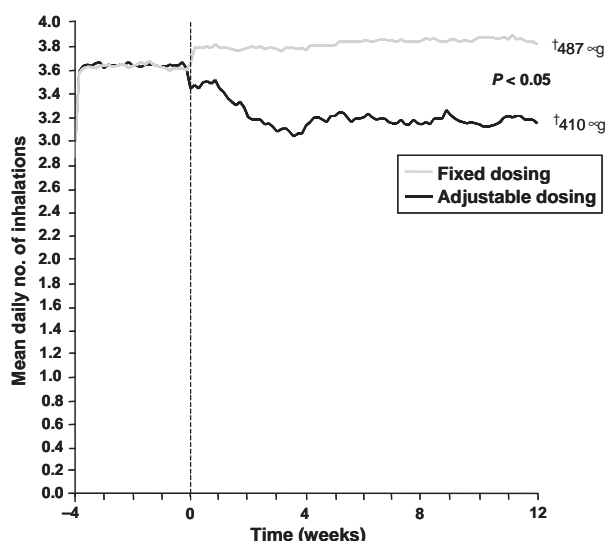


Figure 4 Mean number of inhalations per day of budesonide/formoterol in the adjustable- and fixed-dosing groups. The dashed vertical line indicates baseline at which patients were randomised to the two study groups. †mean daily budesonide dose.

than in the fixed-dosing group (3.2 vs. 3.8, respectively; $P < 0.05$) (Fig. 4); the mean daily ICS dose was 77 µg lower with adjustable dosing during the last 7 days of treatment. The reduction of inhaler use in the adjustable-dosing group occurred mainly during the first 4 weeks of the randomisation period; thereafter the dose was maintained at a similar level. In addition to the reduction in budesonide/formoterol use in the adjustable arm, this group also used 0.2 fewer doses of reliever medication each day than the fixed-dosing group (Table 4). The reliever use in the 604 patients who succeeded in stepping down their dose was 0.74 inhalations per 24 h, and 0.22 (95% CI 0.09–0.35, $P = 0.001$) less than in the fixed-dosing group. Of the patients who reduced their dosage of study medication, 95% did not experience a treatment failure during the 12-week randomised period, and 84% had an improvement in, or maintained, their asthma symptom control.

Safety results

Budesonide/formoterol treatment was well tolerated. During the run-in, 32% of patients experienced AEs and 4% discontinued because of AEs (Table 5). There were two deaths (myocardial infarction; congestive heart failure and coronary

Table 5 Adverse events (AEs) during the study.

<i>n</i> (%) of patients with:	Run-in period (weeks –4 to 0) All treated patients (<i>n</i> = 1719)	Randomised period (weeks 0–12)	
		Adjustable dosing (<i>n</i> = 782)	Fixed dosing (<i>n</i> = 771)
AE	555 (32)	448 (57)	440 (57)
Serious AE	25 (1)	24 (3)	28 (4)
Fatal serious AE	2 (<1)	0	0
AE leading to discontinuation	67 (4)	15 (2)	19 (2)
Due to asthma	15 (<1)	6 (<1)	8 (1)
aggravation			
Most frequently reported AEs			
Upper respiratory tract infection	27 (2)	61 (8)	42 (5)
Respiratory infection	22 (1)	51 (7)	47 (6)
Common cold	29 (2)	48 (6)	45 (6)
Headache	59 (3)	40 (5)	39 (5)
Asthma aggravation	21 (1)	33 (4)	35 (5)
Sore throat	38 (2)	27 (3)	24 (3)
Cough	20 (1)	20 (3)	17 (2)
Accident and/or injury	6 (<1)	14 (2)	20 (3)
Coryza	5 (<1)	12 (2)	14 (2)

insufficiency) during run-in; neither was considered, by the investigators, to be related to treatment.

During the randomised-treatment period, there were no significant differences between groups in the incidence of AEs (57% both groups), serious AEs (4% fixed dosing, 3% adjustable dosing) or discontinuations arising from AEs (2% both groups) (Table 5). The types of AEs reported throughout the study were similar in both groups and within patients using the 80/4.5 or 160/4.5 µg formulation. The most frequently reported serious AE was asthma aggravation (17/24 serious AEs in the adjustable-dosing group, 17/28 in the fixed-dosing group); of these events, six and eight led to withdrawal.

Discussion

The present randomised, controlled study is the first to examine the effect of a symptom-driven, self-management plan in a large asthma population receiving budesonide/formoterol in a single inhaler (Symbicort®). Patients were recruited from a large number of general practices and hospital clinics, and represented a diverse group in terms of severity status and therapy at entry into the study. This study demonstrated that patients were able to adjust their treatment over a four-fold dose range using a simple asthma action plan. Furthermore, in comparison with traditional, fixed twice-daily dosing, adjustable dosing was as effective in terms of symptom severity, treatment failures, and secondary efficacy variables, which included clinic PEF, asthma-free days, nocturnal awakenings, symptom scores, MiniAQLQ, and morning and evening home PEF. Adjustable dosing led to reduced usage of combination therapy resulting in a 16% reduction in inhaled steroid consumption. Unexpectedly, inhaled β_2 -agonist reliever usage was also reduced to a statistically significant degree (0.2 inhalations/day) in the adjustable-treatment arm compared with fixed dosing. Such reduced medication usage can be expected to result in reduced healthcare costs.

The present study incorporated a pragmatic, open-label design to reflect normal clinical practice as far as possible. This was selected in preference to a double-dummy, placebo-controlled design, which would have significantly complicated the nature of the study. Patients were recruited from a large number of general practices and hospital clinics; this makes the results generalisable to patients with a range of asthma severity, on various treatments, from different clinical settings in

different parts of the country. To ensure quality control across the large number of participating centres, there were training sessions before and during the study and regular monitoring, inspection and audit visits during the study. Compliance was not directly measured other than by recording of inhalations taken (on diary cards). Patients in the twice-daily fixed-dosing arm recorded taking an average of 3.8 inhalations daily compared with the prescribed 4.0 inhalations daily. A very small proportion of patients recorded 0 inhalations over short periods reflecting relatively low levels of patient non-adherence, as expected in a clinical trial of this nature.

Although a mix of uncontrolled (59%), and controlled (41%) patients entered the study on an ICS plus a short-acting β_2 -agonist (SABA) reliever or an ICS plus a maintenance LABA, respectively, both types of patients responded well to the 4-week fixed-dose, twice-daily treatment with budesonide/formoterol in a single inhaler. Overall, symptom severity was maintained in 60% and improved in 31% of patients, which was also reflected in a clinically relevant improvement in QoL and PEF, representing greater effectiveness of the study treatment compared with pre-trial medication. While this improvement may be related to better adherence with therapy within a clinical trial, the results are consistent with other clinical studies in which formoterol was added to an ICS in adult patients with asthma.^{6,7} This suggests that an appropriate patient group was selected for study.

Following randomisation, overall asthma control was maintained to an equivalent degree in both treatment groups; only 6% of patients from each group experienced a treatment failure during the 12-week treatment period. The success of budesonide/formoterol was also reflected in the overall shift to a lower asthma symptom severity status during the study, with the majority of the shift from moderate- to mild-persistent or mild-intermittent asthma. The initial improvements in asthma symptoms, QoL and peak flow observed during the run-in period were also maintained in both groups following randomisation. A small, but statistically significant, reduction in morning and evening PEF was seen in the adjustable-treatment arm compared to the control group; however, the difference between groups (4–5 l/min, about 1% of baseline) is not clinically meaningful. In addition, treatment success and failure in patients in the adjustable-dosing group who reduced their dosage of study medication were similar to those for the whole population, suggesting that adjustable dosing did not compromise asthma control.

Patients successfully managed the adjustable-dosing regimen using a single combination inhaler: the majority were able to step up and step down their dose of budesonide/formoterol in response to typical variations in their symptoms. This treatment approach could be convenient for patients and physicians and may minimise the need to visit the doctor for additional prescriptions.

Interestingly, patients who reduced budesonide and formoterol in the adjustable-dosing group also used less reliever medication, suggesting that the use of an asthma action plan, based on adjustable dosing, is an appropriate strategy for optimising therapy. The efficacy and tolerability of budesonide/formoterol in a single inhaler observed in this study was consistent with previous studies evaluating this inhaler in patients with both mild and more severe asthma^{8,9,22,23} as well as extensive previous experience with the two separate component drugs.

A potential limitation of using this subjective self-assessment of symptoms to guide dosage adjustment, is that it did not include an objective PEF measurement, although the value of including lung function within a pragmatic action plan where patient's reported symptoms dictate management is debatable.²⁴⁻²⁶ Furthermore, improvement in patient-based outcome measurements including MiniAQLQ has been shown to be more sensitive than conventional measures of asthma control including PEF and SABA use in a recent study of two formulations of BDP inhalers.²⁷ In the present study, improvements in MiniAQLQ observed during the run-in were maintained throughout the study. Exacerbation rates were similarly low (6%) in both treatment groups, suggesting that the action plan, used for guiding adjustment of budesonide/formoterol dose, was clinically appropriate for this patient group.

One interpretation of our data is that the benefits of adjustable dosing over fixed dosing were achieved because of overtreatment of patients in the fixed-dosing group. However, all the patients entering the study satisfied the criteria according to national and international guidelines for treatment with ICS and LABA, indeed 41% of patients were already receiving LABA, making the question of dosage adjustment particularly appropriate. The marked improvement in asthma control achieved during the run-in on a fixed dose of budesonide/formoterol treatment further justified the use of ICS and LABA in these patients. The question addressed by the study was how adjustable dosing, using the adopted self-management plan, would compare with traditional fixed twice-daily dosing. Randomisation ensured that patients

who might or might not benefit from a reduction in dose were evenly distributed between treatment groups. The pattern of dosage adjustment seen in the study, indicated that many of the patients were not, in fact, overtreated. During the 3-month treatment period, 21% of patients did not meet the criteria for reducing dose and overall 28% stepped up their dose to 8 inhalations daily at least once. Furthermore, of the 79% of patients on adjustable dosing who stepped down during the study, 20% stepped up at least once during the study.

Successful asthma management relies on establishing a partnership between the patient and healthcare professional(s); the aim is to provide the necessary and appropriate education, support, medication and action plans to enable patients to effectively control their own condition.¹ The value of guided self-management is supported by the present large study and previous smaller studies that have shown benefits for asthma self-management plans.^{12,13,28,29} Apart from the present clinical trial programme, we are unaware of other studies of self-management in patients taking a LABA. This strategy needs formal comparison with others aimed at reducing individual components of combination therapy ICS and/or LABA but no validated schemes have been published as yet.

It might be argued that asthma treatment based on symptom control alone might fail to suppress bronchial hyper-responsiveness (and underlying airway inflammation) and fail to prevent airway remodelling,³⁰ and this requires formal long-term testing with a LABA in combination with an ICS. Exacerbation rates would be a clinically relevant measure to study, but will require more patients and/or a longer study to demonstrate any statistically significant differences between treatment regimens.

Further studies^{31,32} are currently in progress as part of the same clinical trial programme with a similar design to the present study; preliminary results³² support the use of adjustable budesonide/formoterol dosing in guided self-management over a 6-month period.

In summary, budesonide/formoterol (Symbicort[®]) treatment rapidly achieved asthma symptom control in a diverse asthma population over a 4-week period and this was maintained throughout the remaining 3 months of the study. An adjustable-dosing regimen with a single inhaler was as effective as a traditional, fixed-dosing regimen in controlling asthma and was as well tolerated at lower overall drug dosages. Budesonide/formoterol in a single inhaler is a logical development for convenience and may enhance compliance by

providing a simple, flexible, convenient, and individualised approach to asthma management consistent with the objectives of therapy within the current BTS/SIGN guidelines.² It should also minimise the need to visit the doctor for additional prescriptions. This study in a large, diverse patient population has demonstrated that self-management, based primarily on symptom parameters, using adjustable dosing of budesonide/formoterol, maintains improved accepted outcomes of asthma control and patient well-being at lower overall doses compared with fixed maintenance dosing.

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